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A Prospective Study of Disease Progression in Patients With Atherosclerotic Renal Artery Stenosis

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The natural history of renal artery stenosis (RAS) has been difficult to document because serial arteriography is rarely justified. Duplex scanning is a noninvasive technique that is ideally suited for both screening and follow-up of RAS. In this approach, renal arteries are classified as normal, <60% stenosis, ≥60% stenosis, or occluded, and disease progression is defined as a change in the duplex classification. The purpose of this study was to determine the rate of disease progression in atherosclerotic RAS by serial duplex scanning. At least one abnormal renal artery was identified in each of 76 patients being screened for RAS. Of the 152 renal arteries, 20 were excluded (14 prior interventions, 5 occlusions, 1 technically inadequate duplex scan), leaving 132 for the natural history follow-up protocol. The patient group included 36 men and 40 women, with a mean age of 67 years, who were followed for a mean of 32 months (maximum 55 months). The initial status of the 132 renal arteries was normal in 36, < 60% stenosis in 35, and ≥ 60% stenosis in 61. The cumulative incidence of progression from normal to ≥ 60% RAS was 0% at 1 year, 0% at 2 years, and 8% at 3 years. The cumulative incidence of progression from < 60% to ≥ 60% RAS was 30% at 1 year, 44% at 2 years, and 48% at 3 years. All 4 renal arteries that progressed to occlusion had ≥ 60% stenoses at the initial visit, and for those arteries with a ≥ 60% stenosis, the cumulative incidence of progression to occlusion was 4% at 1 year, 4% at 2 years, and 7% at 3 years. Progression of RAS occurred at an average rate of 7% per year for all categories of baseline disease combined. Progression of atherosclerotic RAS is relatively common, particularly from < 60% to ≥ 60% stenosis. Am J Hypertens 1996;9:1055–1061

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Atherosclerotic renal artery stenosis is a common cause of secondary hypertension and is also becoming recognized as an important cause of ischemic renal failure.[1–3] Although the indications for renal revascularization in patients with the typical clinical features of renovascular hypertension are generally accepted, intervention for patients with renal artery stenosis associated with controlled hypertension or varying degrees of renal insufficiency is controversial. If the natural

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history of atherosclerotic renal artery stenosis were known, decisions concerning the indications and timing of renal artery interventions could be based on the actual progression rates and risk factors for disease progression.

In contrast to studies of patients after therapeutic interventions, natural history studies require serial follow-up of relatively large numbers of patients who typically do not have clinical indications for invasive diagnostic procedures. Thus, the testing methods used in natural history studies must be safe, reliable, and low in cost. Noninvasive testing methods are ideally suited for such screening and follow-up examinations; however, renal artery lesions could not be identified accurately by noninvasive methods until the development of abdominal duplex scanning.[4–9] The current clinical applications of renal duplex scanning include screening of patients with hypertension or renal failure, follow-up of renal artery interventions, evaluation of renal transplants, and natural history studies.[10–15]

An initial report on the use of duplex scanning to document the natural history of atherosclerotic renal artery stenosis in patients who were not considered candidates for immediate renal revascularization was published in 1994.[14] The present report provides extended follow-up on this group of patients as part of an ongoing effort to determine both the rates and risk factors for renal artery disease progression.

METHODS

In January 1990, a prospective study on the natural history of renal artery stenosis was initiated at the University of Washington Medical Center. Patients were obtained from referrals to the Vascular Diagnostic Service for suspected renal artery stenosis. Indications for renal artery screening were hypertension, decreased renal function, or both. Those patients who were shown to have at least one abnormal renal artery by duplex scanning and who were not considered candidates for immediate surgical or radiologic intervention were eligible for recruitment. This study was approved by the Human Subjects Review Committee at the University of Washington, and informed consent was obtained.

The technique of renal artery duplex scanning has been described in detail previously.[4–6] All examinations were performed with an ATL Ultramark 9 duplex ultrasound system (Advanced Technology Laboratories, Bothell, Washington). Patients were examined after an overnight fast in the supine position using a 2.25 MHz phased array or 3 MHz mechanical transducer. The abdominal aorta was examined first to identify aneurysmal or occlusive disease, and the aortic peak systolic velocity was measured at the level of the superior mesenteric artery. Th right renal artery origin was then identified in a cross-sectional view of the aorta, and velocities were recorded from the origin, proximal, middle, and distal segments. Similarly, the origin of the left renal artery was located, and velocities were recorded throughout its length. The angle of the Doppler ultrasound beam for all renal artery velocity measurements was 60° or less.

The severity of stenosis in each renal artery was classified according to previously validated criteria based on the peak systolic velocity (PSV) in the renal artery and the renal-to-aortic ratio (RAR), which is defined as the ratio of the peak systolic velocity in the renal artery to the peak systolic velocity in the adjacent abdominal aorta.[6] These criteria permit classification of renal artery narrowing into the four categories listed in Table 1: normal (0% diameter stenosis); < 60% diameter stenosis; ≥ 60% diameter stenosis; and occluded. The most severe degree of stenosis found among the origin, proximal, middle, or distal segments of a particular renal artery established the disease category for that side. Disease progression was defined as an increase in stenosis severity to ≥ 60% diameter reduction or the development of total renal artery occlusion, as documented by serial duplex scans. Renal arteries, which were classified as normal or < 60% stenosis at the baseline visit, showed disease progression if they were found to have ≥ 60% stenosis or occlusion on subsequent evaluations. Those arteries with ≥ 60% stenosis at baseline could only progress to occlusion.

As of November 1994, 122 patients have been recruited for the natural history follow-up protocol. Of these, 46 were excluded from this analysis for the following reasons: 27 had not yet undergone any follow-up studies; eight were presumed to have fibromuscular dysplasia rather than atherosclerosis of the renal

TABLE 1. CRITERIA FOR THE CLASSIFICATION RENAL ARTERY DISEASE BY DUPLEX SCANNING

Renal Artery Diameter Reduction	Renal Artery PSV	RAR
Normal (0%)	<180 cm/sec	<3.5
<60%	≥180 cm/sec	<3.5
≥60%	< or ≥180 cm/sec	≥3.5
Occlusion (100%)	No signal	No signal

PSV, peak systolic velocity.

RAR, renal-to-aortic ratio (ratio of peak systolic velocity in the renal artery to the peak systolic velocity in the adjacent abdominal aorta).

If the peak systolic velocity in the abdominal aorta is abnormally low (less than 40 cm/sec), the RAR cannot be used, and identification of a ≥60% renal artery stenosis is based on the finding of a localized high-velocity jet and poststenotic turbulence.

arteries; eight had undergone bilateral renal artery interventions; two had withdrawn from the study after the initial or baseline evaluation; and in one patient an adequate renal duplex scan could not be obtained. The remaining 76 patients contributed 152 potential renal artery sides. Of these, 20 renal arteries were excluded because of prior interventions (14), renal artery occlusion at the baseline evaluation (5), and a technically inadequate duplex scan (1). This left 132 renal arteries for inclusion in the natural history analysis. After the baseline evaluation, patients were followed at 6-month intervals, for those with at least one high-grade ($\geq$ 60% diameter reduction) renal artery stenosis, and at 12-month intervals, for patients with less severe renal artery lesions.

In addition to a complete renal artery duplex scan, clinical information obtained at each baseline and follow-up visit included risk factors for atherosclerosis (smoking, diabetes, or hypercholesterolemia), symptoms or signs of atherosclerotic disease at other sites (coronary, carotid, and lower extremity arteries), and any interventions for treatment of arterial disease. The duration and treatment of hypertension were also documented. Blood pressures were recorded in both arms, and the higher of the two arm blood pressure measurements was used in the analysis. Blood samples for blood urea nitrogen (BUN) and creatinine determinations were drawn at the baseline visit and at yearly intervals thereafter.

Estimates for the cumulative incidence of renal artery disease progression were calculated by life-table analysis using the Kaplan-Meier method. Confidence intervals for progression rates were calculated using the jackknife method.[16] Due to possible dependence of disease progression between the left and right renal arteries within a patient, standard statistical software could not be used to calculate standard errors and confidence intervals. The jackknife method provides an approximate alternative approach to this type of analysis. Confidence intervals (95% level) were calculated as the observed progression rate $\pm$ 1.96 $\times$ the jackknife standard error. Differences in risk factors between patients with and without renal artery disease progression were assessed by χ^2 or Fisher's exact test (categorical risk factors) or by t test (continuous risk factors). For this analysis, a patient was considered as having progressed if progression was noted in either renal artery.

RESULTS

Of the 76 patients who provide the basis for this report, 36 were men with a mean age of 68 years, and 40 were women with a mean age of 66 years. Patients were followed for a mean interval of 32 months, with a maximum follow-up of 55 months. The clinical characteristics of the patient population at the baseline visit were as follows: 34% had a history of myocardial infarction, 9% had intermittent claudication, 11% had undergone a carotid endarterectomy, 11% had diabetes mellitus, 75% were current or former cigarette smokers, and 38% had a history of high serum cholesterol.

Because the protocol required evaluation of both renal arteries in each patient, the recruitment of patients with unilateral renal artery disease resulted in the follow-up of some normal renal arteries. The disease status of the 132 renal arteries on the baseline duplex scan was normal in 36, $<$ 60% stenosis in 35, and $\geq$ 60% stenosis in 61. The majority of the lesions were located at the origin or within the proximal segment of the renal artery.

Seven patients with seven high-grade renal artery lesions had therapeutic interventions during the follow-up period, including six balloon angioplasties and one nephrectomy. In these patients, the analysis of disease progression for a particular renal artery used only the period of observation up to the intervention. All of these interventions were indicated for hypertension that was not adequately controlled on a drug regimen. In addition, three of these patients had deteriorating renal function with a rising serum creatinine. Three patients showed improved blood pressure control after intervention, including the patient treated by nephrectomy. The four remaining patients did not have improved blood pressure control after balloon angioplasty, but two of these patients also had contralateral untreated high-grade renal artery stenoses. None of the treated patients with an elevated serum creatinine has required hemodialysis during the follow-up period.

Disease progression to $\geq$ 60% stenosis or occlusion was observed in 26 renal arteries during follow-up. Of these, 12 renal arteries had a single follow-up evaluation and 14 renal arteries had multiple follow-up evaluations. The disease progression rates and their 95% confidence intervals are presented in Table 2. Values outside the confidence intervals are unlikely in a population of patients such as these. For the life-table analysis of renal artery disease progression, 98 arteries were followed for 12 months, 72 arteries were followed for 24 months, and 53 arteries were followed for 36 months. The cumulative incidence of progression from normal to $\geq$ 60% stenosis was 0% at 12 months, 0% at 24 months, and 8% at 36 months, whereas the cumulative incidence of progression from $<$ 60% to $\geq$ 60% stenosis was 30% at 12 months, 44% at 24 months, and 48% at 36 months. All four renal arteries that progressed to occlusion had $\geq$ 60% stenoses at the baseline evaluation, and for those arteries with $\geq$ 60% stenoses, the cumulative incidence of progression to occlusion was 4% at 12 months, 4% at 24

TABLE 2. CUMULATIVE INCIDENCE OF RENAL ARTERY DISEASE PROGRESSION* ACCORDING TO THE SEVERITY OF DISEASE AT THE BASELINE EVALUATION

Baseline Renal Duplex	Follow-Up Interval			
	0 Months	12 Months	24 Months	36 Months
Normal				
Progression (0.95 CI)	0% (—)	0% (—)	0% (—)	8% (0–19)
n	36	33	27	22
60% Stenosis				
Progression (0.95 CI)	0% (—)	30% (15–45)	44% (25–63)	48% (28–68)
n	35	22	14	11
70% Stenosis				
Progression (0.95 CI)	0% (—)	4% (0–9)	4% (0–9)	7% (0–16)
n	61	43	31	20
All progressions				
Progression (0.95 CI)	0% (—)	10% (5–15)	14% (7–21)	20% (12–28)
n	132	98	72	53

*Disease progression defined as an increase in stenosis severity to ≥60% diameter reduction or the development of total renal artery occlusion (see text).
n = number of renal arteries at beginning of follow-up interval. 0.95 CI = 95% confidence interval calculated by the jackknife method (see text).

months, and 7% at 36 months. Renal artery disease progression occurred at an average rate of 7% per year for all categories of baseline disease combined.

The categorical and continuous risk factors that were assessed for predictive value relative to progression of renal artery stenosis are listed in Tables 3 and 4. No significant relationship could be detected between renal artery disease progression and the individual risk factors of diastolic blood pressure level, serum BUN and creatinine, current or former smoking status, diabetes mellitus, prior myocardial infarction, intermittent claudication, or high cholesterol. However, the following risk factors showed trends toward an association with progression of renal artery stenosis: advanced age, elevated systolic blood pressure, pack-years of smoking, female gender, poorly controlled blood pressure (> 140/90 mm Hg), and a history of carotid endarterectomy.

TABLE 3. ASSOCIATION OF CATEGORICAL RISK FACTORS WITH RENAL ARTERY DISEASE PROGRESSION

Baseline Risk Factor		Percent Showing Disease Progression	P
Gender	Male (36)	31%	.05
	Female (40)	52%	
Blood pressure control	>140/90 (66)	47%	.13*
	≤140/90 (8)	13%	
Current/former smoker	No (19)	42%	NS
	Yes (57)	42%	
Diabetes mellitus	No (68)	40%	.27*
	Yes (8)	62%	
Myocardial infarction	No (50)	40%	.61
	Yes (26)	46%	
Intermittent claudication	No (69)	42%	NS*
	Yes (7)	43%	
Carotid endarterectomy	No (68)	38%	.06*
	Yes (8)	75%	
High cholesterol	No (45)	42%	.90
	Yes (27)	41%	

Sample size in ( ).
* P computed by two-tailed Fisher's exact test.

DISCUSSION

The surgical management of renovascular disease initially focused on hypertensive patients with fibromuscular dysplasia or localized atherosclerosis of the renal arteries. However, during the last decade, an increasing proportion of patients requiring renal revascularization has presented with advanced widespread atherosclerosis and renal insufficiency.[17–19]

TABLE 4. ASSOCIATION OF CONTINUOUS RISK FACTORS WITH PRESENCE OR ABSENCE OF RENAL ARTERY DISEASE PROGRESSION

Baseline Risk Factor	Disease Progression		P
	No Mean ± SD	Yes Mean ± SD	
Age	66 ± 9 (44)	69 ± 8 (32)	.08
Systolic blood pressure	164 ± 22 (43)	171 ± 20 (32)	.15
Diastolic blood pressure	85 ± 7 (43)	85 ± 10 (32)	.87
Blood urea nitrogen	21 ± 10 (32)	26 ± 22 (26)	.26*
Creatinine	1.3 ± 0.6 (32)	1.6 ± 1.6 (26)	.39
Pack-years of smoking	27 ± 30 (39)	39 ± 37 (28)	.14

* Distribution of blood urea nitrogen values is markedly skewed; Mann-Whitney P is 1.00.
Sample size in ( ).

This trend may be due, at least in part, to improved pharmacological treatment of hypertension and cardiovascular disease in general. Percutaneous transluminal balloon angioplasty has been effective in treating fibromuscular dysplasia of the main renal artery, but the long-term results with atherosclerotic lesions have been relatively poor.[20] Thus, the patients currently being considered for renal revascularization tend to have significant medical comorbidity and require complex vascular reconstructions or bilateral renal artery procedures.

Because of the association between renal artery atherosclerosis and similar lesions elsewhere, it is now common to encounter patients with significant renal artery disease who do not have the generally accepted indications for immediate renal revascularization.[21–23] The role of renal artery intervention in patients without uncontrollable hypertension or markedly decreased renal function is uncertain. Such prophylactic intervention for renal artery stenosis can only be justified based on natural history data that include the rate of disease progression in the renal arteries, risk factors for progression, and the overall effect of disease progression on clinical outcome.

Since contrast arteriography has been the only method available for detecting renal artery disease, previous reports on the natural history of renal artery stenosis have included only patients having multiple arteriograms. Wollenweber et al reviewed serial arteriograms on 30 patients and found progression in 50% of the renal artery lesions over a mean follow-up period of 42 months.[24] In a review of 39 patients with atherosclerotic renal artery lesions who underwent arteriography at intervals ranging from 6 months to 10 years, Meaney et al noted an overall progression rate of 36%.[25] Schreiber et al followed 85 patients for a mean period of 52 months and showed progression of renal artery stenosis in 44%.[26] Of these 85 patients, 14 (16%) developed renal artery occlusion, and the risk of progression to occlusion was particularly high in renal arteries with more than 75% stenosis.

In a more recent study, Tollefson and Ernst reviewed 48 patients with 79 atherosclerotic renal artery stenoses who did not have immediate repair and were followed for a mean period of 7.3 years.[27] Progression of stenosis was noted in 42 of the 79 renal arteries (53%), and 7 lesions (9%) progressed to complete occlusion. No renal artery stenoses of < 60% diameter reduction progressed to occlusion, and the average stenosis on the arteriogram immediately prior to occlusion was 80%. The authors concluded that patients with severe, preocclusive renal artery stenoses should benefit from prophylactic renal revascularization during aortic reconstruction.

Because the preceding studies are all retrospective and based on highly selected groups of patients having indications for serial arteriograms, the reported progression rates may not accurately represent those in the general population. However, because arteriography is an invasive test, it is not suitable for prospective follow-up of unselected patients. Prior to the development of renal artery duplex scanning, no noninvasive test was available for assessing the severity of renal artery disease. Although a few unfavorable experiences have been reported,[28,29] duplex scanning is now generally accepted as an accurate noninvasive method for both renal artery stenosis screening and assessing the results of renal revascularization procedures, and the overall accuracy of duplex scanning for identifying renal artery disease is in the range of 80% to 96%.[4–12]

A prospective follow-up study on renal artery stenosis based on duplex scanning has been reported.[14] This study provided data on 80 patients with 139 renal arteries who were followed for a mean period of only 12.7 months. Although none of the initially normal renal arteries showed disease progression, the cumulative incidence of progression from < 60% to ≥ 60% stenosis was 23% at 12 months and 42% at 24 months. All four renal arteries that progressed to occlusion had ≥ 60% stenoses at the baseline visit, and for those sides with a ≥ 60% stenosis, the cumulative incidence of progression to occlusion was 5% at 12 months, and 11% at 24 months. No trends were noted toward an association between the various risk factors analyzed and progression of renal artery disease.

The present study is a continuation of the protocol summarized above to a mean follow-up interval of 32 months. The patient group has been selected to eliminate presumed nonatherosclerotic renal artery disease, renal arteries with prior interventions, and technically inadequate duplex examinations. Patients were eligible for the follow-up protocol if they were not considered candidates for renal revascularization at the time of their baseline evaluation. This selection process was designed to identify those patients with renal artery disease in whom the role of early renal revascularization is particularly uncertain. However, because of this selection process, conclusions based on these data are only applicable to patients with clinical features of atherosclerotic renal artery disease and hypertension, decreased renal function, or both. No definitive statements can be made regarding patients with clinically "silent" renal artery disease.

Retrospective data based on serial arteriography suggests that progression of renal artery stenosis occurs in 30% to 50% of cases.[24–27] In the present prospective study, the overall progression rate of renal artery stenosis was 7% per year. While progression of renal artery disease in renal arteries that were initially normal was rare, the cumulative incidence of progression from < 60% to ≥ 60% renal artery stenosis was 30% at 12 months, 44% at 24 months, and 48% at 36 months. The cumulative incidence of progression from ≥ 60% stenosis to occlusion was 4% at 12 months, 4% at 24 months, and 7% at 36 months.

With the possible exception of female gender, no statistically significant relationship could be detected between any of the categorical or continuous risk factors analyzed and progression of renal artery disease. However, trends toward an increased risk of progression were noted among older individuals, patients with elevated systolic or poorly controlled blood pressure, and patients with a history of carotid endarterectomy. Since the number of patients in many of these risk factor groups is relatively small, it is possible that additional patient recruitment and extended follow-up will eventually establish a predictive value for some of these factors.

Although no definitive clinical recommendations can be made on the basis of this study, it is clear that progression of atherosclerotic renal artery stenosis is common, particularly from < 60% to ≥ 60% stenosis. A relatively low but consistent rate of progression from ≥ 60% stenosis to renal artery occlusion has also been demonstrated. These data suggest that early renal revascularization may be beneficial for selected patients with severe renal artery stenoses; however, the effect of such intervention on further disease progression and clinical outcome remains to be shown. This study is continuing in an effort to find specific risk factors for renal artery disease progression that would identify those patients who would be most likely to benefit from early renal revascularization.

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